PATENT
Attorney Docket No. SER-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Fein, Seymour		
SERIAL NO.:	10/706,100	GROUP NO.:	1654
FILING DATE:	November 12, 2003	EXAMINER:	A. Kosar
TITLE:	*PHARMACEUTICAL COMPOSITIONS INCLUDING LOW DOSAGES OF DESMOPRESSIN*		

Mail Stop Amendments
Commissioner for Patents
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INTERVIEW SUMMARY

On behalf of himself, inventor Dr. Seymour Fein, and Dr. Samuel Herschkowitz, CEO of Serenity Pharmaceuticals Corp., the exclusive licensee of this application, the undersigned attorney thanks Supervisory Patent Examiner Cecilia Tsang, and Primary Examiners Andrew Kosar and Christopher Tate, for their courtesy, consideration, and exchange of views which took place during an in-person interview at the patent office on 9/11/07.

At the interview we discussed the scientific bases of Dr. Fein's invention, reviewed the pending composition of matter claims covering the invention, discussed each of the outstanding rejections, and urged that the claims are patentable. The Examiner's asked many questions and agreed to reevaluate the application in view of new learning presented at the interview. Supervisory Primary Examiner Tsang stated during the interview her belief that there was a "valuable invention present" in this discovery.

The following is a summary of the discussions.

The Invention and the Discoveries Underlying It

At the interview, we urged that Dr. Fein discovered that it is possible to separate the known anti-diuretic effect of desmopressin from its known hyponatremia side effects and that this scientific discovery underlies the claimed composition of matter invention.

We urged that desmopressin in all commercially available and approved formulations cannot function as a safe anti-diuretic because of accompanying occurrence of hyponatremia. This condition, characterized by a low sodium concentration in the blood, occurs in approximately 10-14% of all adult patients who are given desmopressin. Hyponatremia occurs unpredictably within a patient population as well as within each patient. That is, patients who have taken desmopressin without the occurrence of hyponatremia may develop it with subsequent treatment. Prior literature and labeling has always linked its use in adults with this dangerous side effect.

Dr. Fein discovered that anti-diuresis could be *decoupled* from hyponatremia. He administered to water loaded human volunteers (by IV, resulting in 100% bioavailability) known doses of desmopressin, which permitted calculation of desmopressin concentration in the blood. Water loading meant that endogenous vasopressin was not present in the blood of the volunteers and the effect of the blood concentration of desmopressin was isolated. From these studies, Dr. Fein discovered that the threshold blood concentration of desmopressin sufficient to produce an anti-diuresis effect was *much lower* than previously thought. Stated differently, he realized that the prior art used dosage forms that produced blood concentrations that were always unnecessarily high. Dr. Fein suggested that one possible reason for this is the poor bioavailability of desmopressin, a peptide, when administered orally or trans mucosally.

Dr. Fein realized that if one produced a dosage form that established a blood concentration within a low dose range from about 0.1 pg/ml to about 10 pg/ml, that is, *much lower* than ever before disclosed or thought to be efficacious, anti diuresis could be induced for a selected interval of time while the low concentration endured. Further, being an expert in the pharmacokinetics of desmopressin, he knew that its half life is short, about 90 minutes, and therefore realized that natural clearance mechanisms of the

body would be sufficient to reduce the already low desmopressin concentration below the activation threshold. This meant that the anti-diuresis effect could be attained without the expected risk of hyponatremia because normal urine production would commence automatically and blood sodium level would rise naturally. This decoupling enables low dose desmopressin to be administered safely and effectively for new clinical indications, such as adult nocturia, daytime voiding postponement in patients with stress, urge incontinence, and urinary frequency.

Dr. Fein noted that there was a large need for such a formulation and noted that millions of people suffer from nocturia and daytime postponement syndrome. He stated that Serenity Pharmaceuticals Corp. is a small company that needs full and proper patent protection to enable commercialization of this important product.

Dr. Fein further informed the Examiners that many dosage forms could be devised by persons of skill in the art to achieve this blood concentration and its unexpected effect. To protect his invention properly it was critical to obtain low dose desmopressin claims that are unlimited with respect to the chemical or mechanical way the dosage form worked. Rather, the important characteristic of the dosage form is that it is effective to achieve the stated blood concentration range for some desired short period of time, irrespective of how it does so.

The Claimed Subject Matter

Claim 1, as currently pending, states:

> A pharmaceutical composition comprising 0.5 ng to 20 μg desmopressin and a pharmaceutically acceptable carrier in a dosage form adapted for intranasal, transmucosal, transdermal, or intradermal administration sufficient to establishes in a patient a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per mL plasma/serum to about 10.0 picograms desmopressin per mL plasma/serum and to decrease urine production, with the proviso that said dosage form does not produce a desmopressin plasma/serum concentration exceeding about 10 pg/ml.

We urged that this claim (and all other claims pending in the application) meets all requirements of patentability, that the claim is reasonably necessary to adequately protect Dr. Fein's invention, and it is of appropriate scope commensurate with the true scope of his invention.

Provisional Double Patenting

We noted the claims of this application were restricted on April 24, 2006, among composition of matter and process claims. Applicant elected the composition claims here in prosecution. Applicant filed on May 4, 2007 a divisional application containing method claims. Applicant now has received a provisional double patenting rejection of the claims presented here over his divisional application. We submitted that this is improper under 35 USC 121.

35 USC 112 - Lack of Written Description

We noted that in a previous interview with Examiner Tate, the undersigned attorney understood him to suggest that the wording of the claims then pending was insufficient to distinguish from a desmopressin dosage forms which merely *passed through* the claimed blood concentration range on the way to a much higher range. The undersigned noted that the intent as expressed in the specification and the claims was to provide a dose which established, for some reasonable duration, an enduring blood concentration within the range recited in the claim and that significantly higher doses should be avoided as this would raise the specter of hyponatremia development.

In a good faith effort to amend the claim so as to preclude this expansive, unintended interpretation, Examiner Tate and the undersigned discussed the idea that "proviso" language such as that underlined in the claim above might be sufficient to address the Examiner's concern. At that time the undersigned stated that nowhere in the specification was there an explicit statement that the dosage form should not establish a steady plasma/serum desmopressin concentration significantly above 10 pg/ml but urged that adequate basis appeared in the several statements that unequivocally indicated the

dosage form should establish a concentration between about 0.1 pg/ml and 10 pg/ml. Examiner Tate seemed to agree with this. In our reply, in a spirit of compromise, we offered to add the language underlined in the claim set forth above and have now received a lack of written description/new matter rejection.

At the interview of 9/11/07, after presenting this history, we urged that the rejection is improper and that there is a basis for the added language in the specification (see: the abstract, paragraph 11 of the summary, and claim 8 as originally filed, and, for example, MPEP 2173.05, paragraph three). We also stated that in response to the office action we will remove the limitation and if necessary add it as a dependent claim so as to preserve the issue for appeal.

35 USC 103 - Obviousness

We expressed our view that the obviousness rejection is improper. This view was supported by our comments concerning:

- the well recognized need for safe, temporary urine production interruption,
- failure of others to develop a solution to the problem despite the availability of desmopressin for about 30 years,
- the well recognized large market for a pharmaceutical that can safely temporary interrupt urine production, and
- the discoveries underlying the claimed subject matter.

We urged that Dr. Fein has not conducted a "routine optimization" exercise. Rather, he has made an important, unobvious, and valuable invention. Furthermore, we noted that the applied Dixon reference states at page 642:

> We have confirmed in man the finding of others in animals . . . that the minimum effective dose of DDAVP [desmopressin] in hydrated subjects is 2 ng/kg.

> However a dose of this order (200 ng) failed to produce a significant reduction in urine flow rate . . . .

Two ng/kg translates to about 20 pg/ml, or about double the upper limit of the claimed range of hyponatremia-avoiding, antidiuretic effect. This we urged is a *clear teaching away* from applicant's claimed dosage form.

35 USC 102 Anticipation

Examiners Tate and Kosar stated their concern that the language of the claims:

> adapted for intranasal, transmucosal, transdermal, or intradermal administration sufficient to establishes in a patient a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per mL plasma/serum to about 10.0 picograms desmopressin per mL plasma/serum

was insufficient to distinguish the claimed pharmaceutical composition from the disclosures of the various references. We disagreed and urged that this language clearly does distinguish, and that the anticipation rejection is improper. In support of this position, we noted the following:

- applicant's invention does not lie in the particular way (mechanical or chemical) one achieves the blood concentration range, although applicant has limited his claims to exclude oral, subcutaneous, and intra venous dosage forms so as to avoid potential anticipations from unknown sources not of record.

- persons skilled in the art are able readily to make dosage forms without undue experimentation that can easily achieve establishment of the stated blood concentration range. This is particularly true as the key to achieving the new therapeutic effect (anti-diuresis without hyponatremia) is to use *smaller* doses, whereas the art generally has been directed to getting *larger* doses of poorly bioavailable active peptides into the circulation. In this circumstance, it is appropriate to claim a composition "adapted for" administration sufficient to establish the claimed range without reciting in the claim precisely how it is adapted.

- According to the USPTO patent data base, the claims of 484,681 patents use the term "adapted for" and of these 7,853 also use the word "drug." Precedence for the appropriateness of the "adapted for" claim language is found, by way of example only, in the opinion of the court in *Application of Wiggins*, 397 F.2nd 536, (1968). There, the claim was for a pharmaceutical preparation "*adapted for administration to obtain an analgesic effect*" comprising a compound in the range of 10 to 100 milligrams of active, and such a composition "*adapted for oral administration.*" The art disclosed a different dosage form (not containing 10 to 100 milligrams) for a different pharmaceutical use and failed to disclose that the compound had analgesic effect. The court *overruled* the Board of Appeals holding of unpatentability stating:

  > Notwithstanding repeated references by the board as well as the solicitor's brief to appellant's attempt to patent the 'old compositions' shown by [the reference] there seems to be no explicit description [in the reference] of the amounts of [the active compound] employed by appellant.

  In our application the art fails to disclose a dosage form that delivers to the blood the range of active claimed (i.e., a composition within the claims that will establish a blood concentration in the range set forth). The art discloses a different pharmaceutical use (anti-diuresis *linked to* significant hyponatremia risk vs. anti-diuresis *decoupled from* substantial hyponatremia risk). The art fails to disclose the new drug effect (anti-diuresis developed from substantial hyponatremia risk).

- Anticipation is a question of fact. The declaration of the pharmacokinetics expert Dr. Nardi of record in this application, establishes *the fact* that none of the applied references, without modification, disclose or inherently achieve a serum/plasma desmopressin concentration in the claimed range. We referred to the Nardi declaration which explains why this is so at paragraphs 8-17. We urged that none of this declaration is "opinion of [the teaching of] prior art references." None of the *facts* stated by Dr. Nardi are believed to be controversial. In all cases, he attempted to provide fair, factual, opinion-free and scientifically sound explanation of the teachings.

- We urged that the Examiners' repeated assertions that a saline solution designed for IV administration is "adapted for" intra nasal use, for example, is clearly incorrect as it ignores bioavailability differences inherent in different routes of administration. Dr. Fein explained the fundamental differences in dosage, bioavailability and sterility (among other factors) which underlie this position. An IV dose of, say, 200 ng desmopressin as disclosed in Dixon would, if taken trans mucosally, e.g., inhaled, absorbed intranasally, or absorbed sublingually, achieve a blood concentration that was non existent or vanishingly small, not within the stated blood concentration range of the claims, and therefore is not "adapted" to achieve the recited properties. We emphasized that our claims required the composition (dosage form) to be adapted for specific routes of administration which *excluded* IV, sub cutaneous, and oral. We urged that none of the prior art citations conceived of any dosage form that achieved the necessary functional profile nor expressly or inherently disclosed an embodiment of our claimed compositions.

- There was discussion of the applied Stanley et al. patent, which discloses a lollipop formulation designed primarily for the delivery of fentanyl, and includes a disclosure that desmopressin was one of a long list of other drugs that allegedly could be so formulated. We understood Examiner Tate to suggest that given the proper and minimal amount of licks of the lollipop, it would be possible to deliver the proper dosing to produce the same effects as the new functional drug profile of the Fein discovery. Another example of "squirting micro-intravenous doses into the mouth" was also cited. We explained that this was incorrect because the lollipop is inherently a combination transmucosal and oral delivery system which was not able to meet the requirements of our claims and could not achieve the desired decoupling effect. We also referred the Examiners to the previously submitted declaration, paragraph 15, which further explains this. Dr. Fein urged that, in fact, there is no evidence that Stanley ever put desmopressin in a lollipop or generated data of any kind to support utility of his dosage form for desmopressin. We also urged that even if it were possible to achieve the properties of the dosage form claimed using this lollipop formulation, *this reference still would not be sufficient* to support

anticipation by inherency because it fails to meet the legal requirements for a proper inherency rejection.

- More particularly, we urged that none of the references *inherently disclosed* the claimed subject matter as the requirements for a proper 102 rejection based on inherency had not been met. In this regard, more persuasive than our oral argument are the clear provisions of MPEP section 2112, part IV, Requirements of Rejection Based on Inherency – Examiner Must provide Rationale Or Evidence Tending To Show Inherency, quoted in part below (underlining supplied, italics in original):

> The fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) * * * Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.
>
> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

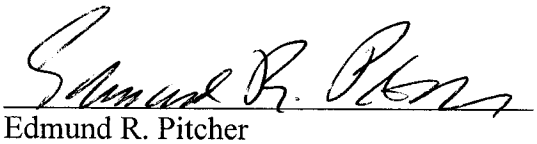
- We also urged that the Examiner's assertion based on the reasoning of MPEP 2112.01, part II (If

The Composition is Physically The Same, It Must Have The Same Properties) was faulty as the assertion that the compositions of the references and the claimed compositions are the same *is incorrect*, as demonstrated by the submitted declaration evidence.

CONCLUSION

Supervisory Primary Examiner Tsang stated during the interview her belief that there was a "valuable invention present" in this discovery. She acknowledged the need to provide proper protection and stated that a method of use patent should be possible. She was undecided as to whether the invention could be protected as a composition of matter, but said that, given the clarification of the new functional properties of the claimed composition and the *Wiggins* case cited, there seems to be ample reason to review the entire case and to revisit this issue. She appeared to recognize that the court in *Wiggins* had deemed that a change in dosing leading to new and unobvious properties could support a composition of matter patent.

Respectfully submitted,



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